Multi-Drug Resistant Gram Negative Infections:

*Therapeutic Approaches in the Emergence of Carbapenem Resistant Enterobacteriaceae (CRE)*

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The information disseminated in this lecture is given in my personal capacity and not in the my capacity as a VA employee nor does it necessarily reflect the views of the United States Department of Veteran Affairs.
1. Identify the spectrum of resistance of carbapenemase-resistant *Enterobacteriaceae* (CRE)

2. Summarize treatment options for CRE infections

3. Review relevant literature on pharmacodynamic dosing interventions and effective combination therapy for CRE infections

4. Recognize the differences between polymyxin B, polymyxin E (Colisitn), and colistimethate sodium (CMS)
Patient Case

Demographics

- 68 yo male
- IBW: 50 kg
- CrCl: 60 mL/min
- WBC = 23
- Tmax 103.6

- AC 68 yo M with hospital acquired pneumonia. On hospital day 6 he is transferred to the ICU with sepsis and respiratory failure. He is ventilated and placed on pressors. CXR shows persistent RLL opacities.

- The medical team initiates amikacin and meropenem due to concern of MDR gram negative pathogen
  - Discontinued: piperacillin-tazobactam
  - Continued vancomycin

- Of note AR has a history of ESBL E. coli UTI and multiple admissions in the last year

IBW = ideal body weight
Patient Case

Infection control alerts the team *K. pneumoniae* is positive for carbapenemases

### BAL sensitivities:

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>K. Pneumoniae</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&gt; 64 R</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥ 32 R</td>
<td></td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>≥ 32 R</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≥ 64 R</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>8 I S</td>
<td></td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>≥ 64 R</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≥ 64 R</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥ 4 R</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;64 R</td>
<td>S</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>≥ 8 R</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≥ 8 R</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-Tazobactam</td>
<td>≥ 128 R</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≥ 16 R</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-Sulfa</td>
<td>≥ 320 R</td>
<td></td>
</tr>
</tbody>
</table>
Carbapenemases

- Bacterial enzyme
- Hydrolyzes **ALL** β-lactams rendering them inactive against the pathogen
  - Penicillin, cephalosporins, cephamycins, monobactams, **AND** CARBAPENEMS
- Carbapenemases are plasmid-mediated
- Contain genes resistant to other antimicrobials
  - Aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole

• Carbapenemases typically isolated in
  - Enterobacteriaceae (*Klebsiella* spp., *E. coli*, *Enterobacter* spp.)
  - *Pseudomonas aeruginosa*
  - *Acinetobacter* spp.

Two distinct types of carbapenemases have been reported in Enterobacteriaceae

1. *Klebsiella pneumoniae* carbapenemase (KPC)
   - Most common carbapenemase in the United States
   - First identified in 2001 North Carolina
   - Ambler molecular class A enzyme: utilizes serine at the active site to facilitate hydrolysis of beta-lactams

Two distinct types of carbapenemases have been reported in Enterobacteriaceae

2. New Delhi metallo-beta-lactamases (NDM-1)

- Rare in the United States
- First identified in a *K. pneumoniae* isolate from a Swedish patient of Indian origin in 2008 who traveled to New Delhi and acquired a UTI
- Detected in India, Pakistan, United Kingdom, Canada, Japan, and U.S.
- Ambler class B metallo-beta-lactamases (MBLs)

Rampant Spread of Resistance:
U.S. Geographical Distribution of Carbapenemase-resistant Enterobacteriaceae (CRE)

2006

2014

Adopted from Centers of Disease Control and Prevention. URL: http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html

Epidemiology of CREs

- Uncommon in the United States before 1992
- An estimated 140,000 healthcare-associated Enterobacteriaceae infections occur in the United States per year
  - Of those 9,300 are caused by CRE
- Up to 50% of bloodstream infections caused by CRE result in death
- Each year, approximately 600 deaths result from CRE infections

Summarize treatment options for CRE infections

Review relevant literature on pharmacodynamic dosing interventions and effective combination therapy

Recognize the difference between polymyxin B, polymyxin E (colistin) and CMS
### CRE Therapeutic Options

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Pharmacodynamic Dosing Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Polymyxin</td>
<td>• Pronlonged, +/- high dose carbapenem infusions</td>
</tr>
<tr>
<td>• Tigecycline</td>
<td>• Double carbapenem</td>
</tr>
<tr>
<td>• Carbapenems</td>
<td>• Combination therapies</td>
</tr>
<tr>
<td>• Aminoglycosides</td>
<td></td>
</tr>
</tbody>
</table>
CRE Therapeutic Options

**GLYCYCYLEINE**

**Tigecycline (Tygacil™)**

**Activity / Use**
- **MDR** – KPC, ESBL, Acinetobacter, MRSA, VRE  
  (Does NOT cover Pseudomonas, Providencia, Proteus sp.)
- Avoid empiric use
- Should NOT be used to treat UTI **OR** as monotherapy in bacteremia and acinetobacter PNA

**Dose**
- Traditional dose: 100 mg IV LD, followed by **50 mg** IV every 12 hours over 30 to 60 minutes
- **High Dose:** 200 mg IV LD, followed by 100 mg IV QD
- Child-Pugh Class C: 100 mg IV LD, followed by **25 mg** IV every 12 hours
- No renal dose adjustment

**Caveats**
- **FDA Alert:** ↑ risk of mortality in hospital-acquired pneumonia (esp. VAP), cSSTI, complicated intra-abdominal, and diabetic foot infections
- Clinical failure reported with KPC infections

**Notes**
- MDR: multi-drug resistant  
- ESBL: extended-spectrum beta lactamase  
- MRSA: methicillin resistant S. aureus  
- VRE: vancomycin-resistant enterococcus  
- KPC: *Klebsiella pneumonia* carbapenemase  
- cSSTI: complicated skin & soft tissue infection  
- LD: loading dose
Therapeutic Approaches

• Summarize treatment options for CRE infections

• Review relevant literature on pharmacodynamic dosing interventions and effective combination therapy

• Recognize the difference between polymyxin B, polymyxin E (colistin) and CMS
High Dose Prolonged Carbapenem Infusions

- **In vitro murine model**
- Doripenem 1 or 2 g every 8 hrs infused over 4 hrs
- Neutropenic mice
  - 1 g dose produced only bacteriostatic response with MICs of 4 to 8 mg/L
  - 2 g dose achieved similar effect for isolates with MICs up to 16 mg/L
- After 24 hrs, ~1 log 10 CFU drop observed in immunocompromised and immunocompetent mice (P < 0.05)

High-dose, prolonged-infusions of doripenem are able to achieve at least bacteriostatic effect in immunocompromised hosts and a modest bactericidal effect in immunocompetent hosts with KPC isolates with MICs up to 8 mg/L

In *vitro* pharmacodynamic model of 11 KPC isolates

Meropenem 2 g every 8 hr over 3 hrs

Bactericidal activity not maintained in 9 of the 11 isolates (81%)

Rapid bactericidal exposure over first 6 hrs against all KPC isolates, regrowth to control levels occurred in 9 of the 11 isolates by 12 to 16 hrs

<table>
<thead>
<tr>
<th>Isolate</th>
<th>MIC</th>
<th>Targeted fT&gt;MIC (%)</th>
<th>Achieved fT&gt;MIC for each dosing interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-8h</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Meropenem provides some efficacy when the MIC is ≤ 2 mg/L despite presence of carbapenemase

Double-Carbapenem Therapy

- KPC isolate (modified Hodge test & blaKPC-3 positive)
  - Doripenem MIC 4 μg/mL, ertapenem MIC 64 μg/mL
- Evaluated doripenem 2 g every 8 hrs infused over 3 hours + Ertapenem 1 g every 24 hrs
- *In vitro* model, regrowth appeared at 24 hours
- *In vivo* thigh infection model, significant bacterial density reduction with doripenem/ertapenem combination vs. doripenem alone
  - 0.9 ± 0.13 log CFU/mL vs. 0.47 ± 0.16 log CFU/mL; \( P = 0.008 \)

### Monotherapy:
- Tigecycline
- Colistin
- Carbapenem

### Synergy Combination Therapy
- Combination of 2 different classes of antimicrobials result in bactericidal activity greater than the sum of either agent alone
  - Tigecycline + Carbapenem
  - Tigecycline + Aminoglycoside
  - Colistin + Carbapenem

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Combination Therapy

• Rationale for combination therapy
  - Maximize the rate and extent of bacterial killing
  - Prevent re-growth
  - Minimize bacterial resistance

• In vitro infection models and animal studies showed optimized combination therapies are highly promising in the treatment of CRE infections

Monotherapy vs. Combination

Hirsch, et al.

- Evaluated 15 studies/reports published from 2004-2009
- Total: 57 Individual treatment courses

Reported Clinical Success Rates

Monotherapy vs. Combination

Qureshi, et al.

Multicenter retrospective cohort study

N = 41 with KPC-producing *K. pneumoniae* Bacteremia

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia (source)</td>
<td>5.7 (0.98 to 3.68)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>∞ (1.59 – ∞)</td>
<td>0.01</td>
<td>Significantly associated with ↑ mortality</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>∞ (0.72 – ∞)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Definitive Combination Therapy</td>
<td>0.07 (0.009–0.71)</td>
<td>0.02</td>
<td>Independent predictor of survival</td>
</tr>
</tbody>
</table>

Results:

Monotherapy vs. Combination

Qureshi, et al.

• Overall Mortality = 38.2%

• Significantly higher rate of mortality among the monotherapy group vs. combination therapy group
  • Monotherapy: 2 of 15 patients
  • Combination: 11 of 19 patients

• Combination therapy may have significant survival benefit

## Definitive Therapy

<table>
<thead>
<tr>
<th>Combination (N = 17)</th>
<th>N(%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tigecycline + Carbapenem</td>
<td>3 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Tigecycline + Aminoglycoside</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Colistin-polymixin B + Carbapenem</td>
<td>2 (33)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Colistin-polymixin B + Tigecycline</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Monotherapy (N=19)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2 (26.3)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Colistin-polymixin B</td>
<td>7 (36.8)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>4 (21)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

**Most successful regimens:**
Combination were either colistin-polymixin B OR tigecycline + carbapenem
• Multicenter retrospective cohort study

• 125 patients with KPC-producing *K. pneumoniae* bloodstream (BSI) infections diagnosed between January 2010 and June 2011

• Primary endpoint: death within 30 days of 1st positive blood culture
Monotherapy vs. Combination

Tumbarello, et al.

- Statistically significantly higher rate of mortality observed among patients treated with monotherapy vs. combination therapy
- Overall 30-day mortality rate = 41.6%

### Monotherapy vs. Combination

**Tumbarello, et al.**

- **Independent Predictors of Mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock at BSI onset</td>
<td>1.04 (1.02 – 1.07)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Inadequate initial antibiotics</td>
<td>4.17 (1.61 – 10.76)</td>
<td>0.003</td>
</tr>
<tr>
<td>High APACHE III score</td>
<td>1.04 (1.02 – 1.07)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postantibiogram therapy with combination tigecycline + colistin + meropenem</td>
<td>0.11 (0.02 – 0.69)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- Post-antibiogram therapy with a combination of tigecycline, colistin, and meropenem is significantly associated with reduced mortality

- Most significant improvement observed with a combination involving a carbapenem

Therapeutic Approaches

• Summarize treatment options for CRE infections
• Review relevant literature on pharmacodynamic dosing interventions and effective combination therapy
• Recognize the difference between polymyxin B, polymyxin E (colistin) and CMS
Polymyxins

• Binds to lipopolysaccharides (LPS) and displaces divalent cations from the outer cell membrane of gram-negative bacteria

• Spectrum: gram negative bacteria
  - No activity against: Neisseria, Proteus, Providencia, Serratia, Burkholderia

• PK/PD best correlates with bactericidal activity: fAUC/MIC

fAUC:MIC = free aurea under the curve: minimum inhibitory concentration
## Polymyxin B vs. Polymyxin E (Colistin)

<table>
<thead>
<tr>
<th></th>
<th>Polymyxin E</th>
<th>Polymyxin B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form administered</strong></td>
<td>INACTIVE PRO-DRUG, CMS (colistimethate sodium)</td>
<td>ACTIVE FORM (polymyxin B sulfate)</td>
</tr>
<tr>
<td><strong>Dose Units</strong></td>
<td>Colistin Base Activity (mg)</td>
<td>International units (10,000 IU/mg)</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>Colistin = non-renal CMS = renal</td>
<td>Non-renal</td>
</tr>
<tr>
<td><strong>Dose Adjustments</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Urinary Concentrations</strong></td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Polymyxins – Toxicity

• Correlated with the TOTAL cumulative amount of CMS

• Nephrotoxicity
  - Estimated 8 to 31%, new data suggesting not as common as previously thought

• Neurotoxicity
  - Paresthesias, visual alterations, ataxia, neuromuscular blockade
  - Typically reversible upon discontinuation
  - Colistin reported rate: 0 – 7%

Polymyxin E (Colistin) Dosing

• No universal dosing for colistin exists
  - Dosing primarily derived from manufacturers’ package inserts

• NOT INTERCHANGABLE
  - Colistimethate sodium, colistin base activity and colistin
  - Products from different manufacturers

• Dose in terms of colistin base activity (CBA)
  - 150 mg of colistin base = 5 million international units of CMS = 400 mg CMS

## Polymyxin E (Colistin) - Various Dosing Approaches

<table>
<thead>
<tr>
<th>Organization</th>
<th>Loading Dose</th>
<th>CrCl (ml/min)</th>
<th>Daily Dose (mg/kg/day)</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PVAMC</strong></td>
<td>--</td>
<td>≥ 80</td>
<td>5</td>
<td>Q6 – 12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 – 79</td>
<td>2.5 – 3.8</td>
<td>Q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 – 49</td>
<td>3.5</td>
<td>Q12 – 24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 – 20</td>
<td>1.5</td>
<td>Q36h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD</td>
<td>1.5</td>
<td>Q24h</td>
</tr>
<tr>
<td><strong>UF Health</strong></td>
<td>3 mg/kg</td>
<td>≥ 70</td>
<td>5</td>
<td>Q8h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 – 70</td>
<td>3.5</td>
<td>Q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 – 29</td>
<td>2.5</td>
<td>Q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10 or HD CRRT</td>
<td>1.5</td>
<td>Q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10 or HD</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>John Hopkins</strong></td>
<td>5 mg/kg</td>
<td>≥ 50</td>
<td>5</td>
<td>Q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 – 50</td>
<td>2.5</td>
<td>Q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 20 or HD</td>
<td>1.5</td>
<td>Q24h</td>
</tr>
<tr>
<td><strong>Cleveland Clinic</strong></td>
<td>Optional 3 mg/kg</td>
<td>≥ 30</td>
<td>4.5</td>
<td>Q8h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 – 30</td>
<td>2.5</td>
<td>Q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 10 or HD</td>
<td>1.5</td>
<td>Q24h</td>
</tr>
</tbody>
</table>
Patient Case

Demographics
- 68 yo male
- IBW = 50 kg
- CrCl: 60 mL/min
- WBC = 23
- Tmax 103.6

- Microbiology reports the following upon request
  - Tigecycline – MIC 2 mcg/mL
  - Colistin – MIC 0.125 mcg/mL

- How would we dose colistin for this patient?
### Patient Case

- **68 yo male,**
- **IBW = 50 kg**
- **CrCl: 60 mL/min**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Loading Dose</th>
<th>CrCl (ml/min)</th>
<th>Daily Dose (mg/kg/day)</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVAMC</td>
<td>-- No Loading Dose</td>
<td>50 – 79</td>
<td>2.5 – 3.8 200 mg/day</td>
<td>Q12h 100 mg Q12h</td>
</tr>
<tr>
<td>UF Health</td>
<td>3 mg/kg 150 mg</td>
<td>30 – 70</td>
<td>3.5 180 mg/day</td>
<td>Q12h 90 mg Q12h</td>
</tr>
<tr>
<td>John Hopkins</td>
<td>5 mg/kg 250 mg</td>
<td>≥ 50</td>
<td>5 250 mg/day</td>
<td>Q12h 125 mg Q12h</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Optional 3 mg/kg 150 mg</td>
<td>≥ 30</td>
<td>4.5 225 mg/day</td>
<td>Q8h 75 mg Q8h</td>
</tr>
</tbody>
</table>
Polymyxin E (Colistin) Suggested Dosing

Garonzik, et al.

• Population PK model for CMS

• Current Enrollment: 105 patients (goal 238 patients)
  - Gram-negative bacilli pneumonia or bacteremia
  - Resistant to meropenem or imipeme, piperacillin-tazobactam, cefepime or ceftazidime, and levofloxacin or ciprofloxacin

• Aim: develop dosing suggestions for CMS based on renal function and desired target steady state plasma concentrations

Polymyxin E (Colistin) Suggested Dosing
Garonzik, et al.

- Steady state level recommendations
  - Target of 2.5 mcg/mL of colistin in plasma
  - For pathogen directed therapy: organisms with MICs ≥ 1 mg/L, a steady state target of 2.5 mcg/mL is unlikely to achieve target AUC:MIC

- Combination therapy recommended, particularly with MICs ≥ 0.5 mg/L and CrCl > 70 ml.min

- Higher maintenance doses of colistin were associated with improved survival in 2 recently published studies

Polymyxin E (Colistin) Suggested Dosing

Garonzik, et al.

• Loading dose (LD) recommended (max of 300 mg)

• Dose by ideal body weight OR actual body weight in kg
  - LD based on CBA (mg) = colistin $C_{ss,\text{avg}}$ target × 2 × body weight (kg)

• Maintenance dose (MD)
  - First MD should be administered 24 hours after the loading dose

• Daily dose of CBA (mg) = colistin $C_{ss,\text{avg}}$ target × (1.5 × CrCl +30)

$C_{ss,\text{avg}}$ target = Average Steady-State plasma concentration
Polymyxin E (Colistin) Suggested Dosing

Garonzik, et al.

- Recommended dosing intervals based on creatinine clearance (CrCl) in mL/min
  - > 70 mL/min: every 8 or 12 hours
  - 10 – 70 mL/min: every 8 or 12 hours
  - < 10 mL/min: every 12 hours

- Calculated based on Jelliffe Equation however Cockcroft and Gault Equation may be used

Polymyxin E (Colistin) Suggested Dosing

Garonzik, et al.

• Intermittent Hemodialysis (IHD)
  - Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 30 mg
  - Supplemental dose of CBA on a HD day add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, **OR** add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
  - Based on 12 patients

• Receiving Continuous Renal Replacement Therapy (CRRT)
  - Daily dose of CBA to achieve each 1.0-mg/L colistin $C_{ss,avg}$ target = 192 mg Doses may be given every 8-12 h.
  - Based on 4 patients

Polymyxin E (Colistin) – Suggested Dosing

Garonzik, et al.

• Studied two manufacturers
  - Paddock Laboratories, Inc. (NDC 0574-0858-01)
  - X-Gen Pharmaceuticals, Inc. (NDC 39822-0615-010)

Polymyxin E (Colistin) – Suggested Dosing

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**Loading Dose:**

\[ \text{CBA (mg)} = \text{colistin } C_{ss,avg \text{ target}} \times 2 \times \text{body weight (kg)} \]

\[ 2.5 \text{ mg/L} \times 2 \times 50 \text{ kg} = 250 \text{ mg} \]

**Maintenance Dose:**

Daily dose of CBA (mg) = colistin \( C_{ss,avg \text{ target}} \times (1.5 \times \text{CrCl} + 30) \)

\[ 2.5 \text{ mg/L} \times (1.50 \times 60 + 30) = 300 \text{ mg/day} \]

CrCl 10 – 70 ml/min: dosing interval Q12h

**FINAL DOSE:** 150 mg IV Q12h
Monitoring Parameters

- Renal function:
  - Serum creatinine (SCr), blood urea nitrogen (BUN), urine output

- Neuromuscular blockade:
  - Depressed respiration, muscle weakness, aspnea
Polymyxin E (Colistin) Drug-Drug Interactions

• Aminoglycosides
  - Increase risk for respiratory depression
  - Nephrotoxicity

• Non-depolarizing neuromuscular blockers (e.g., vecuronium, rocuronium, pancuronium)
  - Enhanced or prolonged neuromuscular blockade
Patient Case

What other agents would we consider to optimize therapy?

• Combination therapy with
  - Meropenem 2 g IV infused over 3 hours every 8 hours
  - Tigecycline 200 mg LD, then 100 mg IV QD

• Minimize the use of other nephrotoxic agents
  - Discontinue vancomycin
  - Discontinue amikacin

SUMMARY

• Infections caused by CREs are resistant to most if not all antibiotics.

• Combination therapy yielded lower rates of mortality compared to monotherapy and should be utilized to treat CRE infections.

• Colistin dosing is **NOT** universal **OR** interchangeable. We must be vigilant when calculating doses, paying close attention to units. Consult Infectious Disease specialist for guidance or hospital dosing policy.
Multi-Drug Resistant Gram Negative Infections:
*Therapeutic Approaches in the Emergence of Carbapenem Resistant Enterobacteriaceae (CRE)*

Diane M. Gomes, Pharm.D.
Outcomes in Antimicrobial Stewardship Post-Doctoral Pharmacy Fellow
Providence Veterans Affairs Medical Center